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AD-A224 232 DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

DTIC ELECTE JUL 17 1990 S D

Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	Unlimited
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: Division of Neuropsychiatry; 6b. OFFICE SYMBOL (If applicable): SGRD-UWI-B	7a. NAME OF MONITORING ORGANIZATION: Walter Reed Army Institute of Research
6c. ADDRESS (City, State, and ZIP Code): Washington, DC 20307-5100	7b. ADDRESS (City, State, and ZIP Code): Washington, DC 20307-5100
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: US Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, MD 21701-5012	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)

Azaprophen, Scopolamine, Trihexyphenidyl, Physostigmine, Acetylcholine receptors, Tolerance

12. PERSONAL AUTHOR(S)
Raymone F. Genovese

13a. TYPE OF REPORT	13b. TIME COVERED FROM _____ TO _____	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
			Approved for public release; Distribution Unlimited

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The effect of the muscarinic acetylchonie receptor antagonists, azaprophen (0.3-10.0 mg/kg), scopolamine (0.01-30 mg/kg) and trihexyphenidyl (0.3-10.0 mg/kg) were examined in rats using a VI 18 s schedule of food reinforcement, before and after chronic physostigmine administration. All three compounds produced dose-dependent increases in the rate of responding. Socolamine was more potent than trihexphenidyl which was equipotent to azaprophen. All three compunds antagonized the response rate-decreasing effects of physostigmine in dose-dependent fashion. Following 43 consecutive daily administrations of physostigmine (0.4 mg/kg), partial tolerance developed to its response rate-decreasing effects. When the three antagonists were again examined (alone and in combination with physostigmine), their effects were generally unchanged. These results further characterize the behavioral effects of azaprophen, scopolamine and trihexphenidyl. These results also sugges that tolerance to physostigmine's effects can be mediated through behavioral rather than pharmacological mechanisms.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION	
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS		
22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL

DD Form 1473, JUN 86 Previous editions are obsolete. SECURITY CLASSIFICATION OF THIS PAGE

European Journal of Pharmacology, 176 (1990) 271–279
Elsevier

EJP 51170

Effects of azaprophen, scopolamine and trihexyphenidyl on schedule-controlled behavior, before and after chronic physostigmine [1]

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Received 1 August 1989, revised MS received 31 October 1989, accepted 21 November 1989

The effects of the muscarinic acetylcholine receptor antagonists, azaprophen (0.3-10.0 mg/kg), scopolamine (0.01-3.0 mg/kg) and trihexyphenidyl (0.3-10.0 mg/kg) were examined in rats using a VI 18 s schedule of food reinforcement, before and after chronic physostigmine administration. All three compounds produced dose-dependent increases in the rate of responding. Scopolamine was more potent than trihexyphenidyl which was equipotent to azaprophen. All three compounds antagonized the response rate-decreasing effects of physostigmine in a dose-dependent fashion. Following 43 consecutive daily administrations of physostigmine (0.4 mg/kg), partial tolerance developed to its response rate-decreasing effects. When the three antagonists were again examined (alone and in combination with physostigmine), their effects were generally unchanged. These results further characterize the behavioral effects of azaprophen, scopolamine and trihexyphenidyl. These results also suggest that tolerance to physostigmine's effects can be mediated through behavioral rather than pharmacological mechanisms.

Azaprophen; Scopolamine; Trihexyphenidyl; Physostigmine; Acetylcholine receptors; Tolerance

1. Introduction

It is well established that the anticholinesterase agent, physostigmine, suppresses responding maintained by schedules of reinforcement in a variety of species, including mice (Wenger, 1979), rats (Rosecrans and Domino, 1974) and pigeons (Vaillant, 1964). It has also been established that chronic administration of physostigmine results in tolerance to many of its effects (Costa et al., 1982) including effects on schedule-controlled behavior (Genovese et al., 1988c; Overstreet and Dubas, 1978). Although the mechanisms of tolerance to physostigmine's effects are not yet clearly understood, previous research has demonstrated that tolerance to physostigmine's effects is not accompanied by changes in blood (Elsmore et al., 1987) or brain (Maayani et al., 1977; Simpson, 1974) acetylcholinesterase activity. Additionally, chronic administration of physostigmine may (Loullis et al., 1981), but does not necessarily (Pinchasi et al., 1977), produce a reduction in muscarinic acetylcholine binding sites, depending upon the degree of physostigmine administration. Similarly, physostigmine-tolerant rats may, but do not necessarily, show a decreased sensitivity to the

[1] In conducting the research described in this report, the investigator adheres to the 'Guide for the Care and Use of Laboratory Animals', as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The views of the author do not purport to reflect the position of the Department of the Army or the Department of Defense (para 4-3, AR 360-5).

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acetylcholine agonist oxotremorine, depending upon the amount and/or schedule of chronic physostigmine administration (Genovese et al., 1988a). The occurrence of tolerance to physostigmine's effects on schedule-controlled behavior depends, in part, on the schedule requirement, but does not depend on pre-session administration (Genovese et al., 1988b). Thus, it is plausible that behavioral compensation (i.e. learning), in contrast to decreases in pharmacological activity, contributes substantially to tolerance to physostigmine's effects.

Previous studies have demonstrated that the effects of physostigmine on schedule-controlled behavior can be attenuated by the administration of acetylcholine antagonists (Genovese et al., 1988c; Wenger, 1979; Vaillant, 1967). Acetylcholine antagonists, however, produce substantial effects on behavior when administered alone (McMaster and Carney, 1986; Williams and White, 1984; Moerschbaecher et al., 1979). Depending upon the point of view, physostigmine can also attenuate the effects of acetylcholine antagonists. For example, Genovese et al. (1988c) found that certain doses of physostigmine and scopolamine, administered separately, produced substantial decreases in the rate of responding of rats under a multiple VI schedule of food presentation, whereas the combination of the two drugs had no effect on response rate.

The primary purpose of the present study was to determine whether the effectiveness of physostigmine for attenuating the effects of acetylcholine antagonists would change as tolerance to physostigmine's effects developed. If tolerance to physostigmine's effects is largely the result of behavioral compensation, then it is hypothesized that no change in the efficacy of physostigmine for attenuating the effects of acetylcholine antagonists would be observed. If, on the other hand, tolerance to physostigmine's effects is accompanied by a decrease in pharmacological activity, a proportional decrease in efficacy for attenuating the effects of acetylcholine antagonists would be expected.

A second purpose of the present study was to assess and compare the effects of three acetylcholine antagonists, scopolamine, trihexyphenidyl and azaprophen. Azaprophen is a novel, conformationally restricted analog of the acetylcholine antagonist atropine. The anticholinergic characteristics of azaprophen have been investigated in a number of in vitro preparations (Caroll et al., 1979) and have been shown to decrease responding under schedules of reinforcement in rats (Witkin et al., 1987) and rhesus monkeys (Genovese and Elsmore, 1989). Azaprophen's novel pharmacological profile suggests that it may have unique anticholinergic properties. Scopolamine is a classical acetylcholine antagonist and has been shown to decrease responding maintained by schedules of reinforcement in rats (Genovese et al., 1988c; McKim, 1979; Wenger, 1979).

Trihexyphenidyl is an acetylcholine antagonist used clinically in the treatment of dystonia, such as the extra-pyramidal effects produced by the administration of antipsychotic agents (Lang, 1986; Fahn, 1983; Burke and Fahn, 1983). It is distinguished from scopolamine and other acetylcholine antagonists in that it has been reported to have euphorigenic effects and considerable abuse liability (Goggin and Solomon, 1979; Pakes and Brotman, 1978; Jellinek, 1977).

2. Materials and methods

2.1. Animals

Twenty-four adult male Sprague-Dawley rats (Hilltop, Scottdale, PA) were used. Rats were individually housed in a temperature controlled environment under a 12 h light-dark cycle. Water was available in the home cages throughout the experiment. Initially, rats were allowed unlimited access to food (Purina Rat Chow) until their body weights reached approximately 320 g. Thereafter, body weights were maintained at 320 g by supplemental feeding occurring several hours after sessions were conducted. Rats had no prior experimental or pharmacological experience.

2.2. Apparatus

Experimental sessions were conducted in 12 standard rodent operant conditioning chambers

(model No. E-10-10; Coulbourn Instruments, Lehigh Valley, PA) housed in ventilated, light- and sound-attenuating cubicles. One wall of the chambers contained two response levers and a food trough that could be illuminated and was attached to a food dispenser capable of delivering 45 mg food pellets (Bioserve, Frenchtown, NJ). Two stimulus lights were mounted above each response lever. Pressing a lever with a downward force of at least 0.3 N was considered a response. Experimental events were controlled and monitored by a PDP-11/73 computer using the SKED-11 software system (State Systems, Kalamazoo, MI).

2.3. Behavioral procedure

Initially, rats were trained to lever-press for food pellets under a CRF schedule of reinforcement. Although two levers were present in each chamber, only one lever produced reinforcement and the position of the active lever (either left or right) was balanced such that in six chambers the left lever was active and in the other six chambers the right lever was active. When lever-pressing was maintained by food presentation, rats were trained to lever-press under a VI 18 s schedule of food reinforcement. Interval values for the VI 18 s schedules were chosen randomly (without replacement) from distributions generated according to the procedure developed by Fleshler and Hoffman (1962) and the range of values was 0.77-62.73 s. Sessions lasted for 30 min and were conducted at approximately the same time each day. During training and initial dose-effect determinations, sessions were conducted daily, Monday-Friday. During and after chronic physostigmine administration, sessions were conducted every day. After approximately 21 sessions under the VI 18 s schedule of reinforcement, performance appeared stable and the rats were assigned to three groups of eight. Groups were matched on the basis of rates of responding with the restriction that each group was balanced with respect to the position of the active response lever.

2.4. Drugs

Azaprophen hydrochloride (0.3-10.0 mg/kg), physostigmine salicylate (0.4 mg/kg), scopolamine hydrobromide (0.01-3.0 mg/kg) and trihexyphenidyl hydrochloride (0.3-10.0 mg/kg) (United States Army Medical Research Institute of Chemical Defense, Aberdeen, MD) were dissolved in 0.9% saline. All injections were administered s.c. in a volume of 1.0 ml/kg body weight. Drug solutions were prepared on the day of injection and all doses are expressed as the salt form.

2.5. Pharmacological procedure

With the exception of chronic physostigmine administration, injections were administered on Tuesdays and Fridays. During dose-effect determinations, before chronic physostigmine administration, data from Thursday's sessions were treated as non-injection controls. Each antagonist was studied in a single group ($n = 8$). The order of drug injections for each group was antagonist and then antagonist plus 0.4 mg/kg physostigmine. Additionally, 0.4 mg/kg physostigmine was administered repeatedly during dose-effect determinations. Doses of the antagonists were administered in a mixed order. After dose-effect functions for the antagonists and the antagonists in combination with physostigmine were determined, 0.4 mg/kg physostigmine was administered daily for 43 consecutive days. Following these sessions, selected doses of the antagonists were again examined, alone and in combination with physostigmine. During this phase of experimentation, physostigmine was administered every day except when an antagonist alone was examined. The dose of physostigmine was chosen on the basis of pilot work and previous research in our laboratories demonstrating that 0.4 mg/kg physostigmine produces a substantial degree of response suppression on schedule-controlled behavior in rats (Genovese et al., 1988a,c). Physostigmine was always administered 10 min before the start of the sessions and the antagonists were administered 40 min before the start of sessions.

2.6. Data analysis

When a response or an experimental event occurred, the elapsed time during the session was recorded. From these data the rate of responding during each session was calculated. To take into account individual variability, response rates were also calculated as a percentage of response rates during non-injection control sessions. Cumulative response records were also generated for each

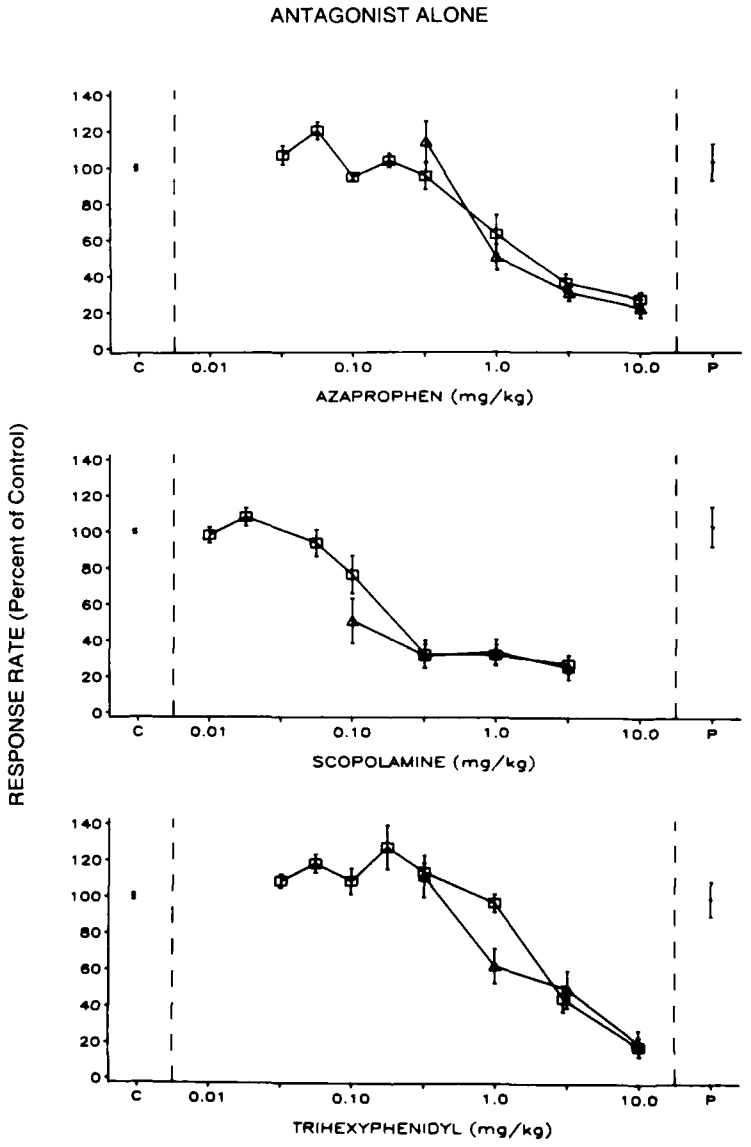

Fig. 1. Effects of azaprophen (top), scopolamine (center) and trihexyphenidyl (bottom), before (squares) and after (triangles) chronic physostigmine administration, in eight rats under a variable interval 18 s schedule of food presentation. Ordinates: response rate as a percentage of control. Abscissas: drug dosage in mg/kg. Points above C represent the mean of six non-injection control sessions. Points above P represent the non-injection control session immediately following the final (post-chronic physostigmine) antagonist administration. Other points represent the mean of single determinations from eight rats. Vertical lines about the points represent ± S.E.M.

session. In order to assess differences in the effects of the antagonists before and after chronic physostigmine, two-factor (dose × time) repeated measures ANOVA, using the normalized rates of responding, were performed for each group.

3. Results

Responding under the VI 18 s schedule of reinforcement was characterized by a relatively constant response rate throughout the entire

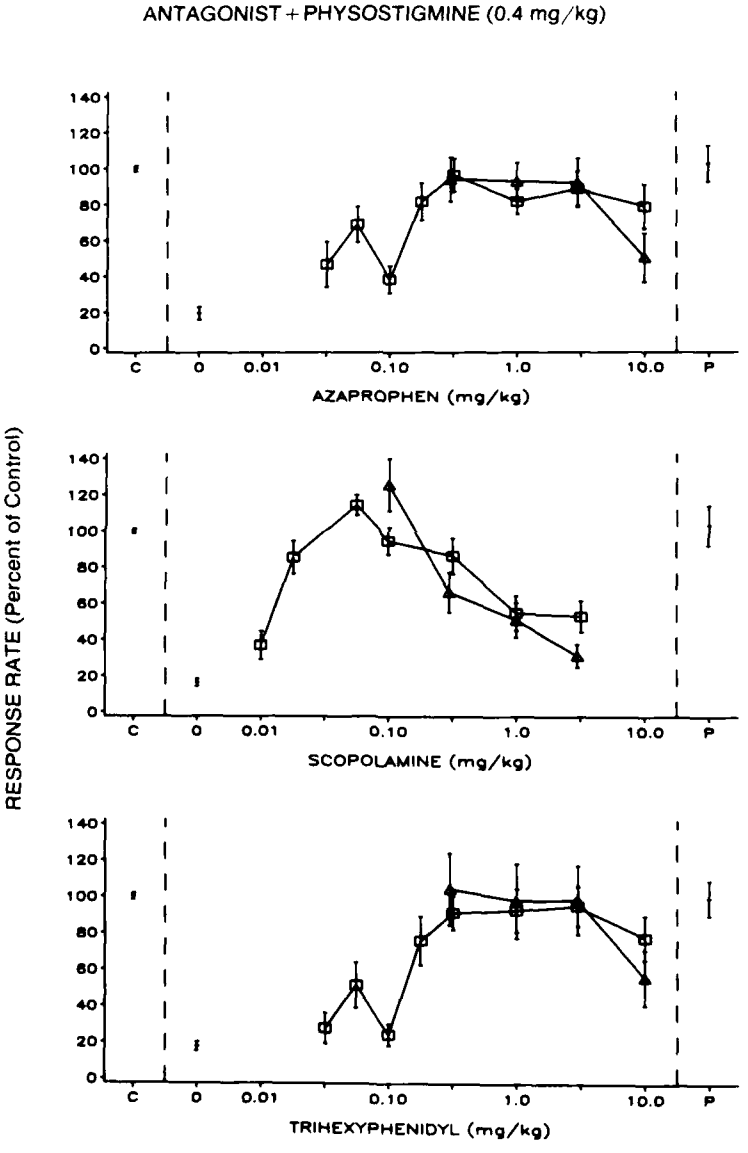

Fig. 2. Effects of azaprophen (top), scopolamine (center) and trihexyphenidyl (bottom), in combination with 0.4 mg/kg physostigmine, before (squares) and after (triangles) chronic physostigmine administration, in eight rats under a variable interval 18 s schedule of food presentation. Ordinates: response rate as a percentage of control. Abscissas: drug dosage in mg/kg. Points above C represent the mean of six non-injection control sessions from eight rats. Points above P represent the non-injection control session immediately following the final (post-chronic physostigmine) antagonist administration. Other points represent the mean of single determinations from eight rats. Vertical lines about the points represent ± S.E.M.

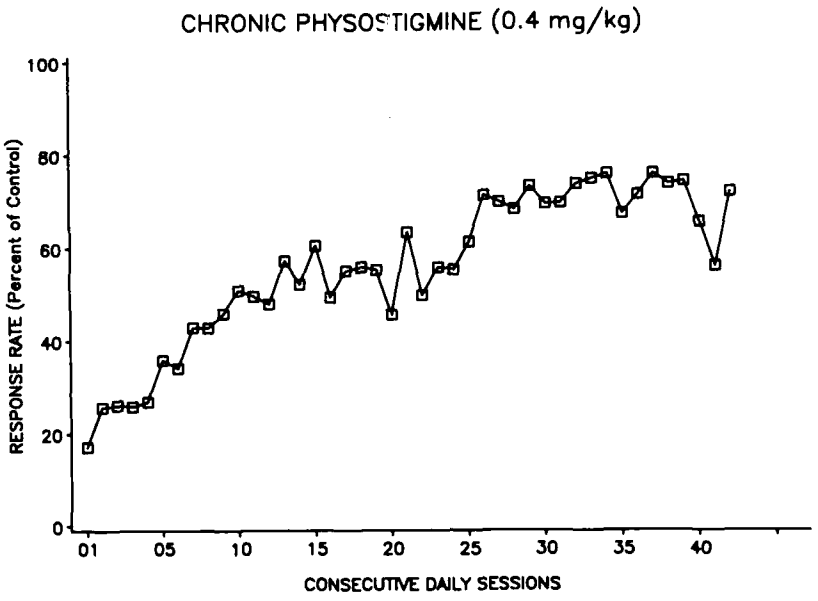

Fig. 3. Effects of chronic daily administration of physostigmine (0.4 mg/kg) in rats under a variable interval 18 s schedule of food presentation. Ordinate: response rate as a percentage of control. Abscissa: consecutive daily sessions. Each point represents the mean of 24 rats.

session. The mean and S.E.M. rate of responding (responses/min) observed during non-injection control sessions during the initial dose-effect determinations for the antagonists were as follows: azaprophen, 90.1 ± 3.4; scopolamine, 74.3 ± 2.8; trihexyphenidyl, 77.9 ± 2.9. The mean and S.E.M. rate of responding for three non-injection control sessions following the initial dose-effect determinations for the antagonists and immediately preceding chronic physostigmine administrations were as follows: azaprophen, 100.4 ± 6.4; scopolamine, 75.9 ± 4.7; trihexyphenidyl, 82.9 ± 5.2. Non-injected control response rates following all drug administrations were similar to those observed during initial dose-effect determinations for the antagonists and before chronic administration of physostigmine (see figs. 1 and 2), demonstrating that pharmacological treatments did not permanently alter the response rate baseline.

When administered alone, scopolamine, trihexyphenidyl and azaprophen produced dose-dependent decreases in the rate of responding (fig. 1). The largest doses of each antagonist administered produced maximal or nearly maximal decreases in response rate in all rats. In this respect, scopolamine was more potent than trihexyphenidyl, which was approximately equipotent to azaprophen. Physostigmine (0.4 mg/kg) administered during initial dose-effect determinations (i.e. before chronic physostigmine administration), reliably produced substantial decreases in the response rates of all rats (fig. 2). All three antagonists produced a dose-dependent attenuation of physostigmine's response-rate-decreasing effects. That is, small doses failed to attenuate physostigmine's effects and larger doses produced a complete or nearly complete antagonism of physostigmine's effects. In the case of scopolamine, large doses administered in combination with physostigmine produced response suppression comparable to that observed when physostigmine was administered alone.

Partial tolerance to physostigmine's response rate-decreasing effects occurred with repeated daily administration (fig. 3). For example, following 43 consecutive daily administrations, the average rate of responding for each group was approximately 65-85% of control values, whereas after the first administration (during the chronic administration phase) the rate of responding was

less than 20% of control values for each group. The difference in response rate between day 1 and day 43, during chronic physostigmine administration, was statistically significant for all three groups (t-tests, $P < 0.05$). When the antagonists were examined after chronic physostigmine administration, their effects when administered alone and in combination with 0.4 mg/kg physostigmine were generally unchanged (figs. 1 and 2). Analyses of variance comparing the effects of each antagonist before and after chronic physostigmine revealed no significant differences for time, when the antagonists were administered alone (azaprophen, $F(1,28) = 0.1$, $P > 0.1$; scopolamine, $F(1,28) = 2.5$, $P > 0.1$; trihexyphenidyl, $F(1,28) = 4.0$, $P > 0.05$), or in combination with physostigmine (azaprophen, $F(1,28) = 0.6$, $P > 0.1$; scopolamine, $F(1,28) = 0.6$, $P > 0.1$; trihexyphenidyl, $F(1,28) = 0.1$, $P > 0.1$).

4. Discussion

The muscarinic acetylcholine antagonists azaprophen, scopolamine and trihexyphenidyl produced dose-dependent decreases in the rate of responding of rats under a VI 18 s schedule of food presentation. These results are in agreement with and extend previous studies demonstrating response suppression effects of acetylcholine antagonists (Genovese et al., 1988c; Wenger, 1979; Vaillant, 1967). Azaprophen, scopolamine and trihexyphenidyl attenuated physostigmine-induced response suppression in a dose-dependent fashion. These results are also in agreement with previous studies that examined the effects of physostigmine in combination with acetylcholine antagonists (Genovese et al., 1988c; Vaillant, 1967). Scopolamine was considerably more potent than either azaprophen or trihexyphenidyl, whether administered alone or in combination with physostigmine. In general, no qualitative differences in effect were observed between any of the antagonists. Since all three antagonists have somewhat different pharmacological profiles, it is surprising that no difference in efficacy for attenuating physostigmine's effects was observed.

Initially, physostigmine produced a marked decreased in the rate of responding under the VI 18 s schedule of reinforcement. With repeated daily administration, partial tolerance developed to physostigmine's effects. These results are in agreement with previous studies demonstrating tolerance to physostigmine's effects on schedule-controlled behavior (Galbicka et al., 1989; Genovese et al., 1988a,b).

When administered alone, the effects of azaprophen, scopolamine and trihexyphenidyl, on response rate were not significantly different before and after chronic administration of physostigmine. In contrast, previous studies have shown that chronic administration of the organophosphorus cholinesterase inhibitor, diisopropylfluorophosphate, increases sensitivity to the behavioral effects of acetylcholine antagonists like atropine (Overstreet et al., 1974; Russell et al., 1971). Previous studies have also demonstrated that chronic administration of long-acting cholinesterase inhibitors, like DFP, reduce the number of muscarinic acetylcholine binding sites. Further, a reduction in muscarinic binding sites is believed to be a major factor mediating tolerance to the anticholinesterase agents (see Russell and Overstreet, 1987). Since sensitivity to the acetylcholine antagonists was not significantly changed following chronic administration of physostigmine in the present study, it is unlikely that a reduction in the number or activity of muscarinic receptors mediated tolerance to physostigmine.

When administered in combination with physostigmine, the effects of all three antagonists on response rate were not significantly different before and after chronic administration of physostigmine. Specifically, the efficacy of physostigmine for attenuating the response rate-decreasing effects of the antagonists was not reduced even though tolerance to physostigmine's response rate-decreasing effects was observed. In this respect, the pharmacological activity of physostigmine was unchanged by chronic administration. This result is consistent with previous studies demonstrating that blood (Elsmore et al., 1987) and brain (Maayani et al., 1977; Simpson, 1974) acetylcholinesterase activity does not correlate with changes in the behavioral effects of

physostigmine during chronic administration regimens. Although muscarinic receptor activity was not specifically measured, this result also suggests that it is unlikely that chronic administration of physostigmine produced down regulation of muscarinic receptors. Taken together, these results suggest that the tolerance to physostigmine's response suppression effects, observed in the present study, was mediated by behavioral compensation rather than a reduction in pharmacological activity. These results complement previous studies suggesting that behavioral compensation can produce tolerance to physostigmine's effects (Genovese et al., 1988a,b). It is notable, however, that multiple processes are probably involved in the development of tolerance to physostigmine's effects, depending upon a number a pharmacological and environmental variables. Behavioral compensation may only be one of a number of processes producing tolerance to physostigmine's effects.

Acknowledgements

The author thanks Timothy F. Elsmore for helpful comments on the design and conduct of the experiment, and Lisa R. King for technical assistance with the conduct of the experiment.

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